REMARKS

Claims 1, 2, 4-7, 30-31, 38-39, 41-45, 47, and 112-113 were pending in the application. New claim 114 has been added. Accordingly, after the amendments presented herein have been entered, claims will be pending.

Support for the new claim can be found throughout the specification and claims as filed. Specifically, support for new claim 114, can be found at, for example, page 10 lines 14-15, page 30 lines 13-14, and Examples 4 and 5.

No new matter has been added. Any cancellation of the claims should in no way be construed as an acquiescence to any of the Examiner's rejections and was done solely to expedite the prosecution of the application. Applicant reserves the right to pursue the claims as originally filed in this or a separate application(s).

Rejection of claims 1-2, 4-7, 30-31, 38-39, 41-47, and 112-113 under 103(a)

The Examiner has maintained the rejection of claims 1-2, 4-7, 30-31, 38-39, 41-47, and 112-113 under 35 USC 103(a) as being unpatentable over 5,859,312 ("Littman et al.") in view of Monbarts et al., McMurry et al., Rowen et al. and Rack et al.

Applicants traverse this rejection for the following reasons.

The Examiner maintains that the claimed invention is unpatentable over Littman et al. in view of Mombaert et al., McMurry et al, Rowen et al. and Rack et al. However, the cited references alone or in combination fail provide the requisite teachings of a non-human transgenic animal capable of producing heterologous T-cell receptors comprising unrearranged human T-cell receptor alpha and beta loci wherein said animal is capable of productive rearrangement of said human T-cell receptor α and β loci.

Littman et al. has a very broad general disclosure that does not enable one of skill in the art to make and/or use transgenic animals carrying human TCR α and β loci that are capable of undergoing productive rearrangement of both TCR α and β loci. The Examiner maintains that McMurry et al. supplements Littman by teaching transgenic mice carrying the human unrearranged TCR delta gene minilocus capable of functionally rearranging. However, McMurry et al. is understood to disclose transgenic mice containing a ***non-productive*** TCR delta gene minilocus. As understood, the minilocus constructs of McMurry contain mutations that change the TCR gene open reading frame and prevent a rearranged TCR transgene from

encoding TCR protein products. See McMurry at pg. 4554 to 4555 (i.e. references 27, 28, including Lauzurica and Krangel provided previously) describing Eδ and Eα miniloci. Specifically, Lauzurica and Krangel provide that in these minilocus constructs, "the Vδ1 and Vγ2 gene segments carry mutations that prevent a rearranged transgene from encoding a functional TCR protein and thereby influencing thymic development" (Lauzurica and Krangel page 1914).

Thus, the transgenic mice generated for the studies of McMurry et al. were intentionally designed to yield artificial non-productively rearranged TCR genes based on the understanding of the authors that productively rearranged TCR genes would unfavorably influence normal thymic development. In light of this, McMurry et al. does not supplement Littman in teaching transgenic mice carrying the human TCR gene loci capable of productive rearrangement in the thymus resulting in expression of human TCRs on T-cells. If fact, based on the teachings of Lauzurica and Krangel that underlie the work of McMurry et al., one skilled in the art would not be motivated to make such a transgenic animal with the knowledge that expression of productively rearranged TCR loci would adversely affect normal thymic development. As previously described, generation of mature T cells with α/β TCRs requires productive TCR loci rearrangement, TCR gene expression and positive/negative T cell selection (via pre-TCR and TCR signaling) in a cell lineage and time dependent manner during thymic development. In addition, Mombaert et al., McMurry et al, Rowen et al. and Rack et al., separately or in combination, do not overcome the limitation of Littman et al. and/or McMurry et al. and do not disclose transgenic animals comprising human TCR α and β loci capable of undergoing productive rearrangement.

Moreover, the cited art disclosing transgenic mice comprising immunoglobulin loci also does not overcome that limitations of Littman et al. and/or McMurry et al. in addressing productive rearrangement of both TCR α/β loci during thymic development and functional expression of TCR α/β on T cells. This cited art relates to transgenic mice capable of expressing soluble Ig by B cells that are derived from a different developmental pathway (i.e. different cell types, organs, timing, signaling complexes and intermediates, gene/loci structures and regulatory elements, etc.) taking place in the fetal liver and bone marrow rather than the thymus. In contrast to the teachings of Lauzurica and Krangel (and McMurry et al.), Applicants have shown

that it is possible to generate mature T cells carrying productively rearranged human T-cell receptor genes in transgenic mice carrying unrearranged human T cell receptor loci.

Lastly, new claim 114 has been added. This new claim is directed to non-human transgenic animals, wherein the human TCR α or β loci contain all of the gene elements. None of the cited references teach or suggest transgenic animals that contain human TCR α or β loci with all the gene elements. Rack et al. is relied on by the Examiner to disclose the human TCR α loci sequence. However, Rack only teaches a construct containing a portion of the TCR α/δ loci gene elements (see, for example, Rack et al. at pages 1233-1234).

Accordingly, based on the foregoing, one of skill in the art would not arrive at the claimed invention by relying on the teachings of Littman et al. McMurry et al., Mombaerts et al., McMurry et al., Rowen et al. and Rack et al. Applicants respectfully request that the Examiner reconsider and withdraw the foregoing rejection.

CONCLUSION

In view of the above amendment, applicant believes the pending application is in condition for allowance.

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Respectfully submitted,

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